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Case Report

Lipoid proteinosis: A multimodal intervention for better aesthetic outcome

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Abstract

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis caused by a mutation in the Extracellular Matrix Protein-1 (ECM-1) gene, leading to the deposition of amorphous hyaline material in the dermis and submucosal connective tissue. The ECM1 gene encodes a structural component of the basement membrane and extracellular matrix. Currently, there is no curative treatment for LP, and management is primarily symptomatic. This article provides a detailed description of a case of LP and a review of existing literature on the various interventional treatment options with their mode of action in LP.

A 20-year-old Asian male presented with generalized disfiguring skin lesions since birth. Clinical examination revealed characteristic findings, including beaded pearly papules along the upper eyelid margins, multiple skin-coloured waxy papules with varioliform scars on the face, and round to oval atrophic scars on the back, chest, and limbs. The diagnosis of LP was confirmed based on histopathological and genetic findings, and the patient was initiated on oral Acitretin at a dose of 25 mg/day. Additionally, the patient underwent fractional carbon dioxide (CO2) laser therapy for atrophic scars every 5 weeks and 4 sessions of intralesional corticosteroid injection for facial papules every 2 weeks. After four months of this combined therapeutic approach, there was significant improvement in both atrophic scars and papules. The patient remains under regular follow-up to monitor progress and manage the condition.

Keywords: Lipoid proteinosis, Fractional CO_2 laser, Aesthetics, Acitretin, Urbach Wiethe Disease, Corticosteroids

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1. Introduction

Lipoid proteinosis (LP), also known as Urbach-Wiethe disease, is a rare autosomal recessive genodermatosis first described in 1929.[1] The disorder is characterized by the deposition of amorphous hyaline-like material predominantly in the skin and mucous membranes, but it can also extend to internal organs, manifesting with a wide range of neurological, psychiatric, and gastrointestinal symptoms.[2] Despite advances in understanding its pathophysiology, LP remains without a cure. Current management strategies are largely symptomatic, with a focus on alleviating systemic symptoms and enhancing the aesthetic appearance of affected individuals. This case report presents a unique instance of LP in a young patient where a novel combination of fractional CO_2 laser therapy, intralesional corticosteroids and oral acitretin demonstrated significant improvement in cutaneous manifestations, offering a potential new strategy in managing this challenging condition.

2. Case Presentation

A 20-year-old Asian male born of a second-degree consanguineous marriage presented with polymorphous skin lesions distributed across his body and face. He sought cosmetic improvement for the face lesions. His medical history revealed a feeble cry with hoarseness of voice at birth. During infancy, he developed fluid-filled lesions and papules over the eyelids and face, that healed with scarring. Over the next few years, similar lesions started to appear on his trunk and limbs, following the same scarring process. At the age of three, the patient underwent surgery to improve his voice quality. Notably, there was no history of developmental delay, family history of similar lesions, photosensitivity, seizures, headache, cognitive defects, visual impairments and difficulty in tongue protruding and swallowing.

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On examination, beaded pearly papules were noted along the upper eyelid margins along with multiple skin-coloured, infiltrated, waxy papules and plaques on the face, predominantly over the forehead and cheeks as in **Figure 1**. Extensive varioliform scars with few deep atrophic scars observed on the face as in **Figure 2** were consistent with a score of 26 points and a severe rating on Goodman and Baron's Quantitative and Qualitative scar scale, respectively. We also noted cobblestone appearance of the hard palate with a diffuse white plaque extending from the hard palate to the soft palate as in **Figure 3**. Additionally, multiple round to oval atrophic scars on the back with scattered papules and scars on the chest and limbs were observed as in **Figure 4**. Systemic examination was unremarkable and laboratory investigations including complete blood count, renal and liver parameters, urine analysis were all within normal limits. Ophthalmic evaluation revealed clear corneas and a normal fundus.

A skin biopsy from a papule on the left elbow demonstrated ortho-keratotic hyperkeratosis and mild acanthosis in the epidermis. The papillary dermis displayed a pathognomonic homogenous eosinophilic, acellular hyaline material extending around the blood vessels in the deeper dermis, which stained positive with Periodic Acid-Schiff (PAS) staining and negative with Congo Red staining as shown in **Figure 5**.

These histopathological findings, combined with the patient's clinical history and examination, confirmed the diagnosis of lipoid proteinosis (LP). Genetic testing further corroborated the diagnosis, identifying a homozygous nonsense variant in exon 7 of the ECM1 gene (chr1:g.150511508C>T; Depth: 237x) that results in a stop codon and premature truncation of the protein at codon 254 (p.Arg254Ter; ENST00000369047.9).

CT brain identified bilateral symmetrical bean-shaped hyperdense foci (x2) of size 13 x 7 mm noted in the mesial temporal lobe, with otherwise normal brain parenchyma as in **Figure 6**.

The patient was counselled on the management options and initiated on oral acitretin at a dose of 25mg daily. To address the atrophic scars and papules on the face, we opted for combined treatment of fractional CO_2 laser 10600nm and intralesional corticosteroids. The patient underwent five laser sessions at 5-week intervals with energy levels gradually increased to optimize outcomes. In the initial session, we utilized 30 mJ pulse energy with 1.5 mm distance, followed by 35mJ with 1.5 mm, 35mJ with 1 mm, 40mJ with 1 mm and 45mJ with 1 mm in the subsequent sessions. The hypertrophic scars and papules on the jawline and chin were treated with 4 sessions of intralesional triamcinolone 5mg/ml at 2-week intervals between the laser sessions.

The patient exhibited significant improvement in facial lesions after 6 months of this combined therapy, as reflected by a reduction in Goodman and Baron Quantitative score to 16 points and a qualitative rating of moderate as seen in **Figure 7**.

He continues to be on regular follow-up and treatment and is on constant monitoring to assess the long-term outcomes and manage any potential recurrence.

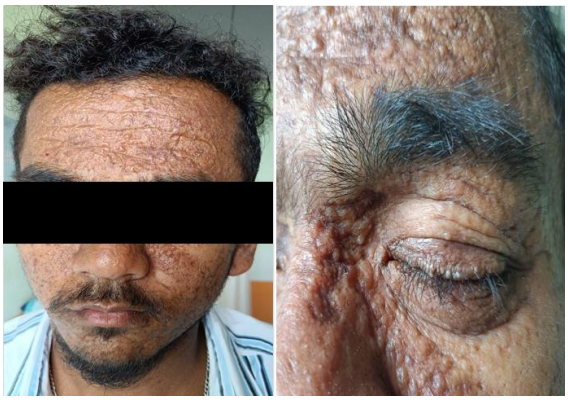

Figure 1: Multiple skin-coloured waxy papules and nodules with atrophic, pock-like scars noted over the face. Beaded pearly papules along the margins of the upper eyelid

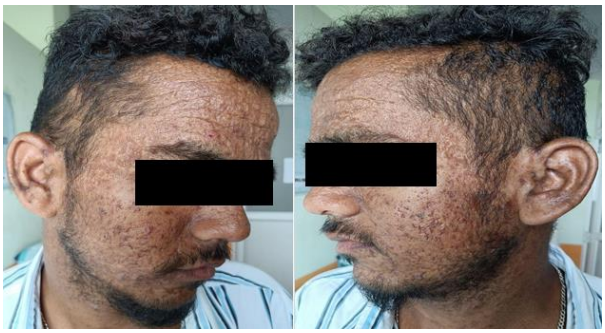

Figure 2: Extensive varioliform scars and papules noted over the face and neck

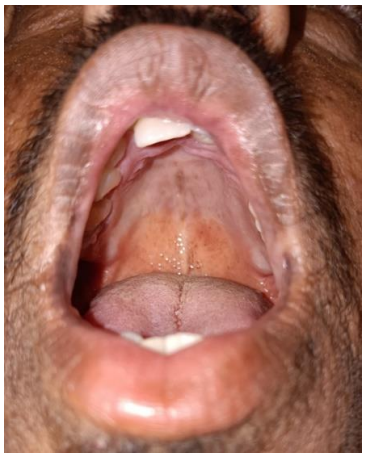

Figure 3: Diffuse white plaque with few papules noted over the hard palate

Figure 4: Multiple round to oval atrophic scars noted over the back

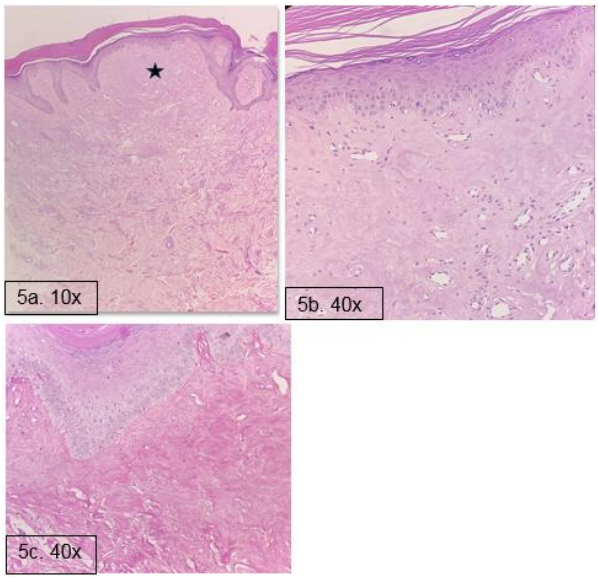

Figure 5: Histopathology shows skin with epidermis showing orthokeratotic hyperkeratosis, mild acanthosis and the underlying papillary dermis shows homogenous eosinophilic, acellular hyaline material with PAS positive, also extending around the blood vessels in the mid and deep dermis. * - amorphous material

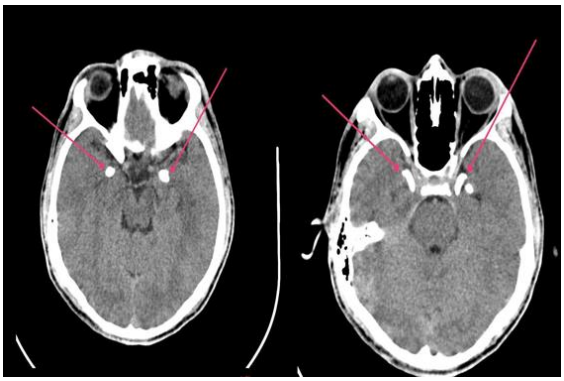

Figure 6: Bilateral symmetrical bean shaped hyper dense foci (x2) of size 13 x 7 mm noted in the mesial temporal lobe.

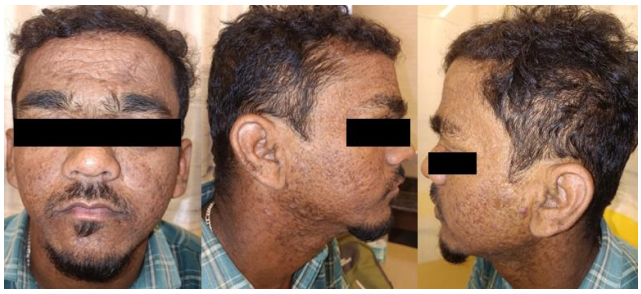

Figure 7: Moderate improvement noted in the papules and atrophic scars according to Goodman and Baron qualitative and quantitative scale.

3. Discussion

Lipoid proteinosis, also known as Urbach-Weithe disease, represents a rare genetic disorder caused by a loss-of-function mutation in the ECM1 gene located on chromosome 1q21 leading to the accumulation of amorphous hyaline-like material in the skin, submucosal connective tissue and internal organs.[1,2] This mutation impacts essential glycoproteins involved in maintaining the structural integrity of the basement membrane and extracellular matrix structure, skin adhesion, and protein-protein interactions.[1] Age at the time of diagnosis is highly variable but the clinical manifestations begin in childhood and affect both sexes equally. The initial presentation often manifests as a weak or hoarse cry at birth, with persistent hoarseness of voice in childhood and a potential airway obstruction due to vocal cords and larynx deposits.[5] Cutaneous changes include skin thickening with a waxy appearance, yellowish papules, pock-like scars, and moniliform blepharosis, a characteristic finding. [2] Oral findings present as cobble stoning of the oral mucosa, thickening of tongue and sublingual frenulum resulting in dysphagia and restricted movements.[2] Neurological involvement manifests as epilepsy, dystonia and cognitive impairment, often observed alongside bilateral symmetric calcification in the temporal lobe or amygdala on CT brain imaging.[4] The diagnosis is based on the typical clinical, histopathological and imaging studies, with blood and serum panels usually within normal limits.

The histopathological features include epidermal hyperkeratosis and a thickened dermis with the presence of large deposits of periodic acid-Schiff (PAS)-positive, diastase-resistant and congo-red negative extracellular hyaline material around blood vessels and appendages.[1] Ultrastructural analysis shows multiple concentric rings of basement membrane around blood vessels and irregular reduplication of the lamina densa at the dermal-epidermal junction.[5]

Despite the absence of a cure, various therapeutic interventions have been explored, primarily aiming to manage symptoms and improve the cosmetic appearance of affected individuals. In our patient, a combination of oral acitretin, fractional CO_2 laser therapy and intralesional

corticosteroids was employed to address the patient's primary concern of facial scarring and papules. Oral retinoids, such as acitretin[6,7] and etretinate,[8] have emerged as a potential therapeutic option in LP. Retinoids are hypothesized to modulate the metabolism of the basement membrane connective tissue matrix.[9] In vitro studies have shown that retinoids suppress the type 3 and 4 collagen synthesis and inhibits the activity of cultured fibroblasts.[9] This proposed potential of acitretin to decrease the hyaline-like material deposition and achieve homeostasis of basement membrane is the rationale for using the drug in this context.

Since the primary concern was the aesthetic appearance and it had significant psychological impact on the patient's QOL fractional CO2 laser therapy with intralesional corticosteroids were utilized. Fractional CO_2 laser therapy was chosen due to its documented success in treating eyelid papules[10] and laryngeal nodules[11] with few reports supporting its use in improving skin appearance in LP. Although the depth of CO_2 laser penetration is said to be 0.02mm theoretically, the depth of fractional micro ablative columns can be increased up to 2mm based on the energy used.[12] As CO_2 laser reaches papillary dermis it is effective in burning off the hyaline like deposits in the dermis. The precision of CO_2 laser with effective zone of coagulation and minimal collateral damage makes it a suitable treatment for the skin scars and papules.[12] Madura et al. employed a novel approach of combining CO_2 laser with radiofrequency (RF) in achieving cosmetic outcomes in LP.[13] However, the drawback of CO_2 laser is the longer downtime and risk of post inflammatory hyperpigmentation, especially in skin of colour.[12] RF works by bulk heating of the mid-to-deep dermal tissues, leading to collagen remodeling and skin tightening, thereby improving the overall clinical appearance.[13]

Alternative laser treatments, such as ErYAG laser has demonstrated favorable outcomes in the facial scars and papules of lipoid proteinosis.[14] Its highest absorption coefficient for water among ablative lasers, results in greater tissue ablation and lesser coagulation which translates to lower treatment downtime. However, a notable disadvantage is the requirement of multiple sessions to achieve optimal results.[14]

Dermabrasion[15] and medium depth to deep chemical peels,[16,17] such as Jessner's peel, 35% TCA, and 80% phenol in water solution have also been explored in the management of lipoid proteinosis. Improving aesthetic appearance with dermabrasion requires precise depth control, for achieving desired results and to prevent scarring, dyspigmentation and milia formation. On the other hand, dermabrasion also has a potential to induce hyaline-like deposits limiting its use.[15] Deep peels, particularly 80% phenol, require cardiac monitoring and involve prolonged downtime, with higher risks of dyspigmentation and scarring, needing cautious use. A case report with a 25-year follow-up highlighted successful aesthetic outcome using dermabrasion combined with Jessner's peel and 35% TCA peels without recurrence of facial lesions.[17]

Systemic treatments including oral dimethyl sulfoxide (DMSO),[18] D-penicillamine,[19] and corticosteroids[16] have shown therapeutic benefits in few cases, though their use is less well-documented in long-term management. D-penicillamine impairs the fibroblast proliferation and inhibits the formation of the cross-links in collagen and elastin fibers.[19] DMSO acts by scavenging hydroxyl radicals and dissolving hydrocollagen[18] and corticosteroids may be effective due to their inhibitory effect on on matrix metalloproteinases (MMP-9) functions.[16]

Human placental extract when administered as an injection and topical application had significant improvement in the appearance of the skin. It is said to be beneficial due to its effect on inflammatory process associated with collagen synthesis.[20]

Topical treatments such as retinoic acid, azelaic acid, corticosteroids have been tried as adjunct therapy.[17] Topical retinoids acts by increasing the cell turnover, exfoliation and aids in neocollagenesis.

Intralesional heparin and corticosteroids and have been tried in a few anecdotal case reports.[17]

Other treatment options include surgical excision,[18] cryotherapy, curettage and electrocauterization of the facial papules and hyperkeratotic lesions.

4. Conclusion

Lipoid proteinosis (LP) typically follows a benign course with a normal life expectancy but the disfiguring facial lesions and systemic manifestations can have a profound impact on the patient's quality of life. Our case highlights the importance of early and appropriate intervention to manage both systemic and aesthetic concerns. In this report, we add a case of LP to the literature, and review the existing literature on various treatment options for LP. Our findings demonstrate a viable, less invasive alternative to achieve significant improvement in a relatively short period, balancing efficacy with patient safety. Nevertheless, the current literature reveals a lack of definitive treatment guidelines for this rare genodermatosis, with most evidence drawn from individual case reports and small case series. Further research and long-term follow-up are needed to refine treatment protocols in LP and explore the potential benefits of combining CO_2 laser therapy with other emerging modalities, which have shown promise in individual case reports.

5. Patient Consent

Consent form patient has been taken prior to the article submission for publication.

6. Data Availability Statement

All data are submitted, additional data can be provided at request

7. Conflicts of Interest

None.

8. Funding of Source

None.

9. Acknowledgements

None.

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